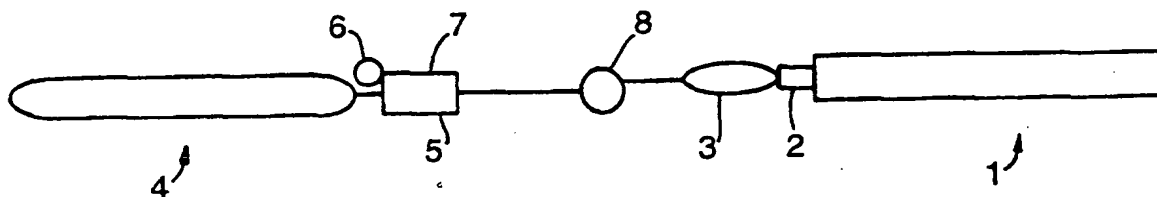




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C12N 15/12, 15/54, 15/62, 15/63, 15/85, 5/10, C07K 14/245, 14/435, 14/47, 14/82, C12Q 1/68 // C12N 15/86, A61K 48/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/12970</b> <b>(43) International Publication Date:</b> 10 April 1997 (10.04.97)
<b>(21) International Application Number:</b> PCT/GB96/02416 <b>(22) International Filing Date:</b> 2 October 1996 (02.10.96)  <b>(30) Priority Data:</b> 9520079.6                      2 October 1995 (02.10.95)                      GB 9616685.5                      8 August 1996 (08.08.96)                      GB  <b>(71) Applicant (for all designated States except US):</b> CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED [GB/GB]; Cambridge House, 6-10 Cambridge Terrace, Regent's Park, London NW1 4JL (GB).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BALMAIN, Allan [GB/GB]; 8 Campsie Dene Road, Blanefield, Glasgow G63 9BN (GB). ZHU, Jingde [CN/GB]; 68 Deveron Road, Glasgow G61 1LN (GB).  <b>(74) Agents:</b> WALTON, Seán, M. et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.          Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: ANTITUMOUR VECTOR CONSTRUCTS AND METHODS



## (57) Abstract

Compositions for targeting expression of a gene such as an antitumor gene may contain a first nucleic acid construct in which expression of a first gene (1) is controlled by a first promoter (2, 3) whose function is suppressed in non-tumour cells, and a second nucleic acid construct in which expression of a second gene (4) for down-regulating the first gene in non-tumour cells is controlled by a second promoter (5, 6) that is up-regulated in non-tumour cells. The second promoter may be regulated by means of p53 binding, targeting expression of the first gene to cells in which p53 down-regulation of expression is disrupted, e.g. cells in which p53 is mutated. The first promoter may be one which is up-regulated in tumour cells, for example the Hsp70 promoter which is up-regulated in mutant p53 tumour cells. A suitable antitumour agent is thymidine kinase, demonstrated using such compositions to provide cell killing action specific for tumour cells as opposed to non-tumour cells.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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GA	Gabon			VN	Viet Nam

## INTERNATIONAL SEARCH REPORT

International Application No.

PC1/GB 96/02416

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C12N15/54 C12N15/62 C12N15/63 C12N15/85  
 C12N5/10 C07K14/245 C07K14/435 C07K14/47 C07K14/82  
 C12Q1/68 //C12N15/86, A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ONCOGENE,  vol. 8, no. 8, August 1993, MACMILLAN  PRESS LTD., LONDON, UK,  pages 2059-2065, XP000616353  Y. SHIIO ET AL.: "Identification of a DNA  element that can enhance p53-mediated  transactivation"  cited in the application  see the whole document</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/-</p>	1-24

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search

27 January 1997

Date of mailing of the international search report

12.02.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3016

Authorized officer

Hornig, H

## INTERNATIONAL SEARCH REPORT

International Application No.

PCI/GB 96/02416

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CELL GROWTH AND DIFFERENTIATION, vol. 6, no. 1, January 1995, WAVERLY PRESS, INC., BALTIMORE, MD, US, pages 1-8, XP000616356 Y. TSUTSUMI-ISHII ET AL.: "Response of heat shock element within the human HSP70 promoter to mutated p53 genes" cited in the application see the whole document ---	1-24
A	MOLECULAR CARCINOGENESIS, vol. 11, no. 3, November 1994, WILEY-LISS, INC. NY, US, pages 127-130, XP000616359 J.D. PITTS : "Cancer gene therapy: A bystander effect using the gap junctional pathway" cited in the application see the whole document ---	1-24
A	ONCOGENE, vol. 9, no. 6, June 1994, MACMILLAN PRESS LTD., LONDON, UK, pages 1791-1798, XP000616357 M. SELVAKUMARAN ET AL.: "Immediate early up-regulation of bax expression by p53 but not TGFbeta1: a paradigm for distinct apoptotic pathways" cited in the application see the whole document ---	1-24
A	GENES AND DEVELOPMENT, vol. 7, no. 12B, 1 December 1993, pages 2556-2564, XP002009095 PAVLETICH N ET AL: "THE DNA-BINDING DOMAIN OF P53 CONTAINS THE FOUR CONSERVED REGIONS AND THE MAJOR MUTATION HOT SPOTS" cited in the application see the whole document ---	1-24
A	MOLECULAR AND CELLULAR BIOLOGY, vol. 15, no. 4, 1 April 1995, pages 1907-1914, XP000564650 DEUSCHLE U ET AL: "TETRACYCLINE-REVERSIBLE SILENCING OF EUKARYOTIC PROMOTERS" see the whole document ---	1-24
A	WO,A,93 15769 (STRATAGENE INC) 19 August 1993 see the whole document ---	1-24

-/--

## INTERNATIONAL SEARCH REPORT

International Application No

PC/GB 96/02416

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 29442 (BASF AG ;BUJARD HERMANN (DE); GOSSEN MANFRED (DE); SALFELD JOCHEN) 22 December 1994 see the whole document ---	1-24
A	WO,A,94 23046 (US HEALTH) 13 October 1994 see the whole document ---	1-24
A	WO,A,95 19367 (JOLLA CANCER RES FOUND) 20 July 1995 see the whole document ---	1-24
A	DE,A,195 02 584 (MEDIGENE GMBH ;ALTMANN HERBERT (DE); WENDLER WOLFGANG (DE)) 3 August 1995 see the whole document -----	1-24

## INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 96/02416

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9315769	19-08-93	CA-A- 2130081	19-08-93
		EP-A- 0671955	20-09-95
		US-A- 5510099	23-04-96
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WO-A-9429442	22-12-94	AU-A- 7108194	03-01-95
		CA-A- 2165162	22-12-94
		EP-A- 0705334	10-04-96
		US-A- 5589362	31-12-96
-----			
WO-A-9423046	13-10-94	AU-A- 6498294	24-10-94
-----			
WO-A-9519367	20-07-95	US-A- 5484710	16-01-96
-----			
DE-A-19502584	03-08-95	AU-A- 1662595	15-08-95
		WO-A- 9520652	03-08-95
-----			

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/

09/051159

## PCT

## CHAPTER II

## DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND
<b>Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION</b>		Applicant's or agent's file reference SMW/BP5257977
International application No. PCT/GB96/02416	International filing date (day/month/year) 2 OCTOBER 1996 (02/10/96)	(Earliest Priority date (day/month/year)) 2 OCTOBER 1995 (02/10/95)
Title of invention ANTITUMOUR VECTOR CONSTRUCTS AND METHODS		
<b>Box No. II APPLICANT(S)</b>		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)  CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED CAMBRIDGE HOUSE 6-10 CAMBRIDGE TERRACE REGENT'S PARK LONDON NW1 4JL UNITED KINGDOM		Telephone No.:  Facsimile No.:  Teleprinter No.:
State (i.e. country) of nationality: GB		State (i.e. country) of residence: GB
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)  BALMAIN Allan 8 CAMPSIE DENE ROAD BLANEFIELD GLASGOW G63 9BN UNITED KINGDOM		
State (i.e. country) of nationality: GB		State (i.e. country) of residence: GB
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)  ZHU Jingde 68, DEVERON ROAD GLASGOW G61 1LN UNITED KINGDOM		
State (i.e. country) of nationality: CN		State (i.e. country) of residence: GB



Further applicants are indicated on a continuation sheet.

International application No.  
PCT/GB96/02416

### Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person ☒ agent ☐ common representative  
is

- and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
- ☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
- ☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WALTON, SEÁN M. and others  
Mewburn Ellis  
York House  
23 Kingsway  
London WC2B 6HP  
GB

Telephone No.:  
0171 240 4405

Facsimile No.:  
0171 240 9339

Teleprinter No.:  
22762 PATENT G

- ☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

### Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the International Preliminary Examining Authority\*

- (i) ☒ to start the international preliminary examination on the basis of the international application as originally filed.
- (ii) ☐ to take into account the amendments under Article 34 of
- ☐ the description (amendments attached).
  - ☐ the claims (amendments attached).
  - ☐ the drawings (amendments attached).
- (iii) ☐ to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).
- (iv) ☐ to disregard any amendments of the claims made under Article 19 and to consider them as reversed.
- (v) ☐ to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

\* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed, or where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination, as so amended.

### Box No. V ELECTION OF STATES

- ☒ The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)* except

*(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)*

International application No.  
PCT/GB96/02416**Box No. VI CHECK LIST**

The demand is accompanied by the following documents for the purposes of international preliminary examination:

## 1. amendments under Article 34

description : 0 sheets

claims : 0 sheets

drawings : 0 sheets

## 2. letter accompanying amendments under Article 34 : 0 sheets

## 3. copy of amendments under Article 0 sheets

## 4. copy of statement under Article 0 sheets

## 5. other (specify) : 0 sheets

For International Preliminary  
Examining Authority use only

received

not received

☐☐☐☐☐☐☐☐☐☐☐☐☐☐

The demand is also accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney4. ☒ fee calculation sheet2. ☐ copy of general power of attorney5. ☐ other (specify):3. ☐ statement explaining lack of signature**Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE**

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

.....

WALTON, SEÁN M.  
APPOINTED AGENT

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

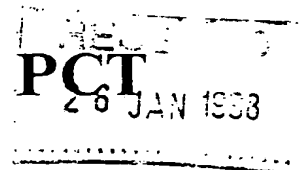
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.☐ The applicant has been informed accordingly.4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.55. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

09/051159

## PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

WALTON, Sean M.  
MEWBURN ELLIS  
York House  
23 Kingsway  
London WC2B 6HP  
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF  
INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing  
(day/month/year)

21. 01. 98

Applicant's or agent's file reference

SMW/BP5257977

## IMPORTANT NOTIFICATION

International application No.

PCT/GB 96/02416

International filing date (day/month/year)

02/10/1996

Priority date (day/month/year)

02/10/1995

Applicant

CYCLACEL LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA;



European Patent Office  
D-80298 Munich  
Tel. (+49-89) 2399-0, Tx: 523656 epmu d  
Fax: (+49-89) 2399-4465

Authorized officer

C. Vullio

Telephone No.

8052

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>SMW/BP5257977</b>		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/GB 96/ 02416</b>	International filing date (day/month/year) <b>02/10/1996</b>	Priority date (day/month/year) <b>02/10/1995</b>	
International Patent Classification (IPC) or national classification and IPC <b>C12N15/12</b>			
Applicant <b>CYCLACEL LIMITED et al.</b>			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


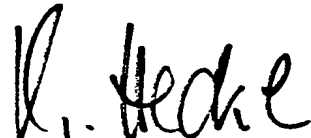
2. This **REPORT** consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of \_\_\_\_\_ sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand <b>17/04/1997</b>	Date of completion of this report <b>21. 01. 98</b>
Name and mailing address of the IPEA:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer <b>K. Heckl</b>  Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/GB96/02416

I. Basis of the report

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

☒ the international application as originally filed.

☐ the description, pages \_\_\_\_\_, as originally filed,  
pages \_\_\_\_\_, filed with the demand,  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

☐ the claims, Nos. \_\_\_\_\_, as originally filed,  
Nos. \_\_\_\_\_, as amended under Article 19,  
Nos. \_\_\_\_\_, filed with the demand,  
Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

☐ the drawings, sheets/fig \_\_\_\_\_, as originally filed,  
sheets/fig \_\_\_\_\_, filed with the demand,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

☐ the description, pages \_\_\_\_\_.

☐ the claims, Nos. \_\_\_\_\_.

☐ the drawings, sheets/fig \_\_\_\_\_.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/GB96/02416

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 2, 3, 5, 7, 9, 17-19	YES
	Claims 1, 4, 6, 8, 10-16, 20-24	NO
Inventive Step (IS)	Claims 17-19 partially	YES
	Claims 2, 3, 5, 7, 9, 17-19 partially	NO
Industrial Applicability (IA)	Claims 1-24	YES
	Claims	NO

2. CITATIONS AND EXPLANATIONS

1. 1. The following documents are considered relevant prior art:

D1: Oncogene 8, 1993, 2059-2065

D2: Cell Growth & Differentiation 6, 1995, 1-8

D3: Mol.Cell.Biol. 15/4, 1995, 1907-1914

D4: WO94/29442

2. Novelty (Art.33(2) PCT):

- 2.1 It has been noted that the present application refers to an approach of cancer therapy which approach uses a dual system; the specific up-regulation of an anti-tumour gene in one construct in tumour-cells and specific down-regulation of the gene in non-tumour cells and the down regulation in non-tumour cells being mediated by a second construct.

However, the claims have to be subjected to IPER as they stand. Therefore, the IPEA has come to the following

opinion:

- 2.2 D1 - D4 disclose compositions and cells containing the two nucleic acid constructs of claim 1 (see D1, abstract and introduction, results, Fig.4-6, materials and methods; D2, abstract and introduction, results, Fig.1-3, materials and methods; D3, abstract and introduction, results, Fig.1, materials and methods; D4, page 2, line to page 4, line 31) which fall under the scope claims 1, 4, 6, 8, 10-16 and 20-24.

3. Inventiveness (Art.33(3) PCT):

- 3.1 Again, in the absence of the true and essential features of the above identified approach, claims 2, 3, 5, 7 and 9 have to be regarded as not being delimited to this approach. Therefore, the features of these claims seem to represent standard embodiments and cannot contribute to inventiveness.
- 3.2 The cited prior art (see the international search report) and the prior art referred to in the description includes various reports on the possible role of diverse genes in the origin of malignancies and within the related field of regulation of transcription. Nevertheless, the above identified approach seems novel and not derivable from the cited prior art.

Since the means to achieve this approach seem to be truly reflected by claims 17-19, as far as being dependent from claim 14, an inventive step can be acknowledged for claims 17-19, partially.

4. For the assessment of the present claims 22 and 23 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The EPO, for example does not allow methods of treatment practiced on

the human or animal body (Art.52(4) EPC). The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VIII. Certain observations on the international application

---

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. It has been noted that the present application refers to an approach of cancer therapy which approach uses a dual system; the specific up-regulation of an anti-tumour gene in one construct in tumour-cells and specific down-regulation of the gene in non-tumour cells and the down regulation in non-tumour cells being mediated by a second construct.

However, claims 1-16, 17-19 as far as not being dependent from claim 14 and claims 20-24 do not truly reflect this approach. Accordingly, these claims lack the essential and true features of the invention (Art.6 PCT, lack of clarity).

2. Moreover, these claims comprise subject-matter which is not part of the present application (Art.6 PCT, lack of support).

## PATENT COOPERATION TREATY

PCT

PTO/PCT Rec'd 02 APR 1998

09/051159

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>SMW/BP5257977</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 96/ 02416</b>	International filing date (day/month/year) <b>02/10/1996</b>	(Earliest) Priority Date (day/month/year) <b>02/10/1995</b>
Applicant <b>CANCER RESEARCH CAMPAIGN TECHNOLOGY LTD et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
  - ☐ filed with the international application.
  - ☒ furnished by the applicant separately from the international application,
    - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
  - ☐ Transcribed by this Authority
4. With regard to the title, ☒ the text is approved as submitted by the applicant.
  - ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
  - ☒ the text is approved as submitted by the applicant.
  - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
  - Figure No. 1 ☒ as suggested by the applicant. ☐ None of the figures.
  - ☐ because the applicant failed to suggest a figure.
  - ☐ because this figure better characterizes the invention.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 96/ 02416

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 22,23  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark: As far as claims 22 and 23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 96/02416

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C12N15/54 C12N15/62 C12N15/63 C12N15/85  
C12N5/10 C07K14/245 C07K14/435 C07K14/47 C07K14/82  
C12Q1/68 //C12N15/86,A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ONCOGENE, vol. 8, no. 8, August 1993, MACMILLAN PRESS LTD., LONDON, UK, pages 2059-2065, XP000616353 Y. SHIIO ET AL.: "Identification of a DNA element that can enhance p53-mediated transactivation" cited in the application see the whole document</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-24

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

27 January 1997

Date of mailing of the international search report

12.02.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3016

Authorized officer

Hornig, H

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 96/02416

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CELL GROWTH AND DIFFERENTIATION, vol. 6, no. 1, January 1995, WAVERLY PRESS, INC., BALTIMORE, MD, US, pages 1-8, XP000616356 Y. TSUTSUMI-ISHII ET AL.: "Response of heat shock element within the human HSP70 promoter to mutated p53 genes" cited in the application see the whole document ---	1-24
A	MOLECULAR CARCINOGENESIS, vol. 11, no. 3, November 1994, WILEY-LISS, INC. NY, US, pages 127-130, XP000616359 J.D. PITTS : "Cancer gene therapy: A bystander effect using the gap junctional pathway" cited in the application see the whole document ---	1-24
A	ONCOGENE, vol. 9, no. 6, June 1994, MACMILLAN PRESS LTD., LONDON, UK, pages 1791-1798, XP000616357 M. SELVAKUMARAN ET AL.: "Immediate early up-regulation of bax expression by p53 but not TGFbeta1: a paradigm for distinct apoptotic pathways" cited in the application see the whole document ---	1-24
A	GENES AND DEVELOPMENT, vol. 7, no. 12B, 1 December 1993, pages 2556-2564, XP002009095 PAVLETICH N ET AL: "THE DNA-BINDING DOMAIN OF P53 CONTAINS THE FOUR CONSERVED REGIONS AND THE MAJOR MUTATION HOT SPOTS" cited in the application see the whole document ---	1-24
A	MOLECULAR AND CELLULAR BIOLOGY, vol. 15, no. 4, 1 April 1995, pages 1907-1914, XP000564650 DEUSCHLE U ET AL: "TETRACYCLINE-REVERSIBLE SILENCING OF EUKARYOTIC PROMOTERS" see the whole document ---	1-24
A	WO,A,93 15769 (STRATAGENE INC) 19 August 1993 see the whole document ---	1-24
	--- -/--	

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 96/02416

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 29442 (BASF AG ;BUJARD HERMANN (DE); GOSSEN MANFRED (DE); SALFELD JOCHEN) 22 December 1994 see the whole document ---	1-24
A	WO,A,94 23046 (US HEALTH) 13 October 1994 see the whole document ---	1-24
A	WO,A,95 19367 (JOLLA CANCER RES FOUND) 20 July 1995 see the whole document ---	1-24
A	DE,A,195 02 584 (MEDIGENE GMBH ;ALTMANN HERBERT (DE); WENDLER WOLFGANG (DE)) 3 August 1995 see the whole document -----	1-24

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 96/02416

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9315769	19-08-93	CA-A-	2130081	19-08-93
		EP-A-	0671955	20-09-95
		US-A-	5510099	23-04-96
-----				
WO-A-9429442	22-12-94	AU-A-	7108194	03-01-95
		CA-A-	2165162	22-12-94
		EP-A-	0705334	10-04-96
		US-A-	5589362	31-12-96
-----				
WO-A-9423046	13-10-94	AU-A-	6498294	24-10-94
-----				
WO-A-9519367	20-07-95	US-A-	5484710	16-01-96
-----				
DE-A-19502584	03-08-95	AU-A-	1662595	15-08-95
		WO-A-	9520652	03-08-95
-----				

FORM PTO-1390  
(REV 10-96)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

CCI-005US

**TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C.371**

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

PRIORITY DATE CLAIMED

02 October 1995 (02.10.95)

INTERNATIONAL APPLICATION

PCT/GB96/02416

INTERNATIONAL FILING DATE

02 October 1996 (02.10.96)

TITLE OF INVENTION

ANTITUMOUR VECTOR CONSTRUCTS AND METHODS

APPLICANT(S) FOR DO/EO/US

Allan BALMAIN and Jingde ZHU

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C.371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371 (f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371 (b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date. **(enclosed) (3 sheets);**
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). **(unexecuted) (4 sheets);**
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included
13. ☒ A **FIRST** preliminary amendment. **(5 sheets);**  
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: **Transmittal Letter (2 sheets duplicate); PCT Request (6 sheets); PCT International Published Application (WO 97/12970) (with International Search Report) (94 sheets); PCT/RO/105 (1 sheet); PCT/IB/301 (3 sheets); PCT/IB/304 (1 sheet); PCT/IB/308 (2 sheets); PCT/IB/306 (1 sheet); PCT International Preliminary Examination Report (7 sheets); Certificate of Express Mailing (1 sheet); and Return Postcard.**

COPY

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)		INTERNATIONAL APPLICATION NO. <b>PCT/GB96/02416</b>		ATTORNEY'S DOCKET NO. <b>CCI-005US</b>	
17. <input checked="" type="checkbox"/> The following fees are submitted: <b>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):</b> Search Report has been prepared by the EPO or JPO.....\$930 International preliminary examination fee paid to USPTO (37 CFR 1.482).....\$720 No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....\$790 Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....\$1070 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....\$98  <div style="text-align: center;"><b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b></div>				<b>CALCULATIONS    PTO USE ONLY</b>	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
<b>CLAIMS</b>	<b>NUMBER FILED</b>	<b>NUMBER EXTRA</b>	<b>RATE</b>		
Total claims	<b>24</b> -20 =	<b>4</b>	X \$22.00	<b>\$88</b>	
Independent claims	<b>1</b> -3 =	<b>0</b>	X \$82.00	<b>\$0</b>	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ 270.00	\$	
<b>TOTAL OF ABOVE CALCULATIONS =</b>				<b>\$1018</b>	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28)				\$	
<b>SUBTOTAL =</b>				<b>\$1018</b>	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
<b>TOTAL NATIONAL FEE =</b>				<b>\$1018</b>	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				\$	
<b>TOTAL FEES ENCLOSED =</b>				<b>\$1018</b>	
				Amount to be: refunded	\$
				charged	\$

- a. ☒ A check in the amount of \$ 1018 to cover the above fees is enclosed.
- b. ☐ Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \$ \_\_\_\_\_ to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 12-0080. A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

**Amy E. Mandragouras**  
**LAHIVE & COCKFIELD, LLP**  
 28 State Street  
 Boston, Massachusetts 02109  
 United States of America  
 (617)227-7400

SIGNATURE

Amy E. Mandragouras

NAME

36,207

REGISTRATION NUMBER

COPY

## PATENT COOPERATION TREATY

PCT

09/051159 20.

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SMW/BP5257977	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB 96/ 02416	International filing date (day/month/year) 02/10/1996	Priority date (day/month/year) 02/10/1995
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant CYCLACEL LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


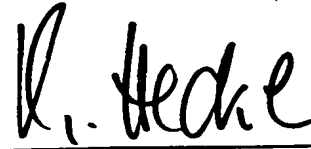
2. This **REPORT** consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of \_\_\_\_\_ sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 17/04/1997	Date of completion of this report 21. 01. 98
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer K. Heckl  Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/GB96/02416

I. Basis of the report

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

☒ the international application as originally filed.

☐ the description, pages \_\_\_\_\_, as originally filed,  
pages \_\_\_\_\_, filed with the demand,  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

☐ the claims, Nos. \_\_\_\_\_, as originally filed,  
Nos. \_\_\_\_\_, as amended under Article 19,  
Nos. \_\_\_\_\_, filed with the demand,  
Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

☐ the drawings, sheets/fig \_\_\_\_\_, as originally filed,  
sheets/fig \_\_\_\_\_, filed with the demand,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

☐ the description, pages \_\_\_\_\_.  
☐ the claims, Nos. \_\_\_\_\_.  
☐ the drawings, sheets/fig \_\_\_\_\_.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/GB96/02416

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 2, 3, 5, 7, 9, 17-19	YES
	Claims 1, 4, 6, 8, 10-16, 20-24	NO
Inventive Step (IS)	Claims 17-19 partially	YES
	Claims 2, 3, 5, 7, 9, 17-19 partially	NO
Industrial Applicability (IA)	Claims 1-24	YES
	Claims	NO

2. CITATIONS AND EXPLANATIONS

1. 1. The following documents are considered relevant prior art:

D1: Oncogene 8, 1993, 2059-2065  
D2: Cell Growth & Differentiation 6, 1995, 1-8  
D3: Mol.Cell.Biol. 15/4, 1995, 1907-1914  
D4: WO94/29442

2. Novelty (Art.33(2) PCT):

- 2.1 It has been noted that the present application refers to an approach of cancer therapy which approach uses a dual system; the specific up-regulation of an anti-tumour gene in one construct in tumour-cells and specific down-regulation of the gene in non-tumour cells and the down regulation in non-tumour cells being mediated by a second construct.

However, the claims have to be subjected to IPER as they stand. Therefore, the IPEA has come to the following

opinion:

- 2.2 D1 - D4 disclose compositions and cells containing the two nucleic acid constructs of claim 1 (see D1, abstract and introduction, results, Fig.4-6, materials and methods; D2, abstract and introduction, results, Fig.1-3, materials and methods; D3, abstract and introduction, results, Fig.1, materials and methods; D4, page 2, line to page 4, line 31) which fall under the scope claims 1, 4, 6, 8, 10-16 and 20-24.

3. Inventiveness (Art.33(3) PCT):

- 3.1 Again, in the absence of the true and essential features of the above identified approach, claims 2, 3, 5, 7 and 9 have to be regarded as not being delimited to this approach. Therefore, the features of these claims seem to represent standard embodiments and cannot contribute to inventiveness.

- 3.2 The cited prior art (see the international search report) and the prior art referred to in the description includes various reports on the possible role of diverse genes in the origin of malignancies and within the related field of regulation of transcription. Nevertheless, the above identified approach seems novel and not derivable from the cited prior art.

Since the means to achieve this approach seem to be truly reflected by claims 17-19, as far as being dependent from claim 14, an inventive step can be acknowledged for claims 17-19, partially.

4. For the assessment of the present claims 22 and 23 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The EPO, for example does not allow methods of treatment practiced on

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/GB96/02416

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the human or animal body (Art.52(4) EPC). The patent-ability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

---

VIII. Certain observations on the international application

---

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. It has been noted that the present application refers to an approach of cancer therapy which approach uses a dual system; the specific up-regulation of an anti-tumour gene in one construct in tumour-cells and specific down-regulation of the gene in non-tumour cells and the down regulation in non-tumour cells being mediated by a second construct.

However, claims 1-16, 17-19 as far as not being dependent from claim 14 and claims 20-24 do not truly reflect this approach. Accordingly, these claims lack the essential and true features of the invention (Art.6 PCT, lack of clarity).

2. Moreover, these claims comprise subject-matter which is not part of the present application (Art.6 PCT, lack of support).

## PATENT COOPERATION TREATY

09/051159

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

To:

WALTON, Seán, M.  
Mewburn Ellis  
York House  
23 Kingsway  
London WC2B 6HP  
ROYAUME-UNI

RECEIVED

26 AUG 1997

Date of mailing (day/month/year)

18 August 1997 (18.08.97)

Applicant's or agent's file reference

SMW/BP5257977

International application No.

PCT/GB96/02416

## IMPORTANT NOTIFICATION

International filing date (day/month/year)

02 October 1996 (02.10.96)

1. The following indications appeared on record concerning:



the applicant



the inventor



the agent



the common representative

Name and Address

CANCER RESEARCH CAMPAIGN  
TECHNOLOGY LIMITED  
Cambridge House  
6-10 Cambridge Terrace  
Regent's Park  
London NW1 4JL  
ROYAUME-UNI

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:



the person



the name



the address



the nationality



the residence

Name and Address

CYCLACEL LIMITED  
Marquis House  
67-68 Jermyn Street  
London SW1Y 6NY  
ROYAUME-UNI

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:



the receiving Office



the International Searching Authority



the International Preliminary Examining Authority



the designated Offices concerned



the elected Offices concerned



other:

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

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Authorized officer

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## PATENT COOPERATION TREATY

PCT/GB96/

09/051159

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE  
COMMUNICATION OF THE INTERNATIONAL  
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

WALTON, Seán, M.  
Mewburn Ellis  
York House  
23 Kingsway  
London WC2B 6HF  
ROYAUME-UNI

RECEIVED

21 APR 1997

Date of mailing (day/month/year)

10 April 1997 (10.04.97)

Applicant's or agent's file reference

SMW/BP5257977

## IMPORTANT NOTICE

International application No.

PCT/GB96/02416

International filing date (day/month/year)

02 October 1996 (02.10.96)

Priority date (day/month/year)

02 October 1995 (02.10.95)

Applicant

CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU,BG,BR,CA,CN,CZ,DE,EP,FI,IL,JP,KP,KR,LC,NO,PL,RO,SK,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AL,AM,AP,AT,AZ,BA,BB,BY,CH,CU,DK,EA,EE,ES,GB,GE,HU,IS,KE,KG,KZ,LK,LR,LS,LT,LU,LV,  
MD,MG,MK,MN,MW,MX,NZ,OA,PT,RU,SD,SE,SG,SI,TJ,TM,TR,TT,UA,UG,UZ,VN

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 10 April 1997 (10.04.97) under No. WO 97/12970

## REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

## REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

J. Zahra

Telephone No. (41-22) 730.91.11

Continuation of Form PCT/IB/308

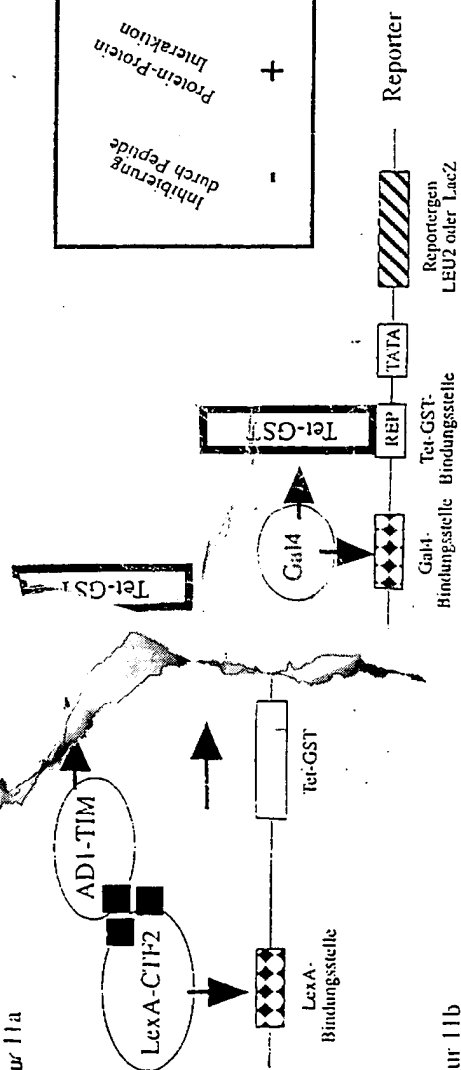
NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF  
THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year) 10 April 1997 (10.04.97)	IMPORTANT NOTICE
Applicant's or agent's file reference SMW/BP5257977	International application No. PCT/GB96/02416

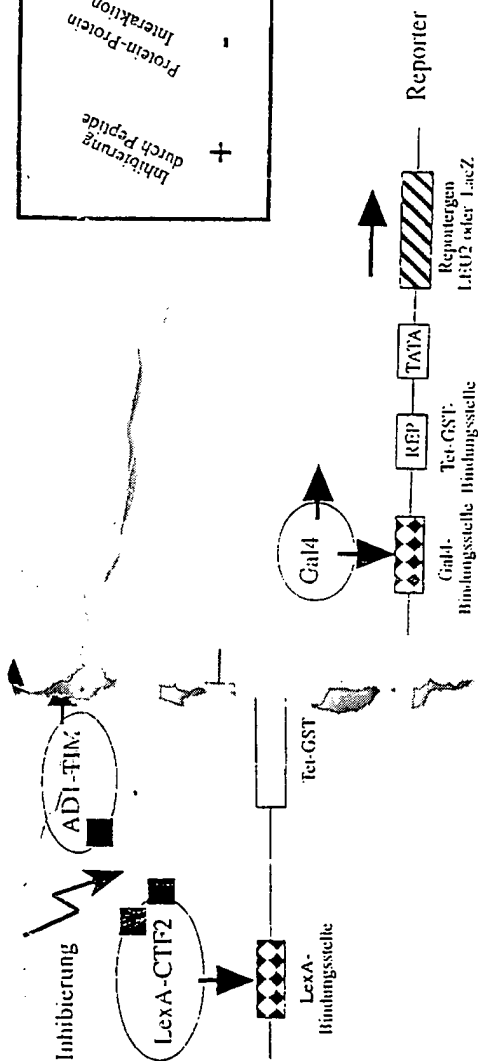
The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

# Repression der Protein-Protein Wechselwirkung zwischen LexA-CTF2 und AD1-TIM im Repressor-abhängigen Verfahren

Figur 11a



Figur 11b



Inhibierung durch Peptide	-
Protein-Protein Interaktion	+
Aktivierung durch AD1-TIM	+
Tet-GST Expression	+
Bindung von Tet-GST	+
Wachstum auf Leucin-defizientem Medium	+
Blau auf X-Gal	+

Inhibierung durch Peptide	+
Protein-Protein Interaktion	-
Aktivierung durch AD1-TIM	-
Tet-GST Expression	-
Bindung von Tet-GST	-
Wachstum auf Leucin-defizientem Medium	+
Blau auf X-Gal	+